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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,999	09/07/2006	Daniel Portnoy	BERK-017CIP	6366

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/547,999	PORTNOY ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1-11-08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-34* is/are pending in the application.

4a) Of the above claim(s) *16-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9-7-05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/07; 6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed 1-11-08 has been entered into the record.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Information Disclosure Statement

The information disclosure statements filed 2-2-07 and 6-15-07 have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election without traverse of Group I, claims 14, 15 and 25-34 in the response filed 1-11-08 is acknowledged.

Claims 16-24 are withdrawn from consideration as drawn to non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 15, 25, 26, 27, 28, 29, 30, 31, 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim requires eliciting or busting a cellular immune response to "an antigen" in a subject, however no antigen is recited in the claims. Therefore it is unclear how the *Listeria* cells provide for a cellular immune response to an antigen when there is no antigen administered or recited in the claims. Clarification is requested.

Claim Rejections - 35 USC § 102 or 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14, 25, 29, 30, 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al (Proc. Nat. Acad. Sci, USA, 92:3987-3991, April 1995; of record on 1449).

Shen et al teach a plasmid integration vector capable of site specific *Listeria* genome integration (see page 3987, column 2, see plasmid construction, delivery to the *Listeria monocytogenes* genome) and how to make such using particular restriction endonucleases. The vector comprises a site-specific plasmid with a heterologous coding sequence and multiple clone sites (i.e as a derivative of pBR322). The vector was prepared using pBR322 as a base and thus necessarily possesses multiple cloning sites because pBR322 has multiple cloning sites. The vector was used to transform *Listeria* monocytogenes by electroporation and provides for the culturing of the transformants for

expression of a heterologous polypeptides and administered as a vaccine for a particular virus (see page 3998, column 1, animal experiments and page 3989, column 2).

Claims 14, 15, 25, 29, 30, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel et al (US Patent No. 6,099,848, issued August 8, 2000).

Frankel et al teach attenuated *Listeria* and their use as a vaccine vector expressing a heterologous protein wherein the DNA encoding the heterologous antigen is stably integrated into the *Listeria* chromosome by homologous recombination. The preferred method for producing a recombinant *Listeria* having a gene encoding a heterologous antigen integrated into the chromosome thereof, is the induction of homologous recombination between a temperature sensitive plasmid comprising DNA encoding the antigen and *Listeria* chromosomal DNA. Stable transformants can be isolated. The method of homologous recombination is advantageous in that site directed insertion of DNA encoding the heterologous antigen is effected, thereby minimizing the possibility of disruption of other areas of the *Listeria* chromosome which may be essential for growth of this organism (column 8, line 6 to column 9, line 22). Frankel et al teach that the vaccine expressing the integrated heterologous antigen can be administered to an animal so as to provide for a cellular immune response (se claims 1-6; and columns 9-13). As such, Frankel et al anticipate the claimed invention.

Claim 14, 15, 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel et al (US Patent No. 6,099,848, issued August 8, 2000) in view of Frazao et al (WO 99/07861, published 18 February 1999) and Loessner et al (Molecular Microbiology, 35(2):324-340, 2000).

Frankel et al teach attenuated Listeria and their use as a vaccine vector expressing a heterologous protein wherein the DNA encoding the heterologous antigen is stably integrated into the *Listeria* chromosome by homologous recombination. The preferred

method for producing a recombinant *Listeria* having a gene encoding a heterologous antigen integrated into the chromosome thereof, is the induction of homologous recombination between a temperature sensitive plasmid comprising DNA encoding the antigen and *Listeria* chromosomal DNA. Stable transformants can be isolated. The method of homologous recombination is advantageous in that site directed insertion of DNA encoding the heterologous antigen is effected, thereby minimizing the possibility of disruption of other areas of the *Listeria* chromosome which may be essential for growth of this organism (column 8, line 6 to column 9, line 22). Frankel et al teach that the vaccine expressing the integrated heterologous antigen can be administered to an animal so as to provide for a cellular immune response (se claims 1-6; and columns 9-13). Frankel et al differ by not teaching the elements of listerophage integrase gene and attachment sites or a tRNAarg integration site.

Frazao et al teach the production of a nucleic acid plasmid vector pAV1 that can direct the insertion of heterologous DNA into a specific site ($tRNA^{Ala}$ gene) of the Mycobacterial genome. The DNA vector includes the attachment site region (attP) and the integrase gene of the mycobacteriophage Ms6. Heterologous DNA linked to this DNA fragment can be carried into the mycobacterial genome through a site-specific integration mechanism (see Figure 7, pAV1) that contains heterologous DNA (ampicillin resistance, Kan/Neo resistance), origin of replication, restriction cloning sites and the *att-int* region of the mycobacteriophage MS6. Frazao et al teach that the integrative vectors and the integrating process described are not restricted to mycobacteria and are applicable to other bacteria such as *Listeria spp.* (page 7, first full paragraph). Frazao et al differs by not teaching the nucleic acid regions for a listeriophage and integration into a Listeria spp..

Loessner et al teaches the complete nucleic acid sequence of the genome structure of bacteriphage A118 of *Listeria monocytogenes*. Loessner et al teaches the bacteriophage integrase gene and a bacteriophage attachment site that integrates into a *Listeria* host gene that is homologous to comK of *Bacillus subtilis* (see abstract, page 324).

Listeria species and comprises a bacteriophage integrase gene and bacteriophage attachment site, multiple different cloning sites, provides for coding of multiple open reading frames (i.e. the polypeptides). Loessner et al teach that the virus is capable of transduction and is able to transduce functional genetic markers into susceptible cells. Loessner et al teach *Listeria* transformed with the vector as a prophage (see page 324, column 1) and specifically describe the region corresponding to the integrase and attP site (see page 328, column 1 and Figure 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made modify the pAV1 of Frazao et al by substituting the integrase gene and attP site of the A118 bacteriophage of *Listeria monocytogenes* according to Loessner et al for the attachment site region (attP) and the integrase gene of the mycobacteriophage Ms6 of the pAV1 of Frazao et al and transduce attenuated *Listeria* of Frankel with the modified vector of Frazao and Loessner et al for the production of heterologous antigens in vivo by administering the site specific modified attenuated *Listeria* spp expressing a heterologous antigen for the generation of a cellular immune response to antigen because Frazao et al teach that exogenous DNA can be linked to this region to provide for site-specific integration into the genome and that Frazao et al teach that the integrative vectors and the integrating process described is not restricted to mycobacteria and is specifically applicable to other bacteria such as *Listeria spp.* (page 7, first full paragraph) and Frankel et al teach that the preferred method for producing a recombinant *Listeria* having a gene encoding a heterologous antigen integrated into the chromosome thereof and that the vaccine expressing the integrated heterologous antigen can be administered to an animal so as to provide for a cellular immune response.

Status of the Claims

Claims 14, 15, 25-34 stand rejected. Claims 16-24 are withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645